



Short communication

Coexisting huntingtin and SCA8 repeat expansion: Case report of a severe complex neurodegenerative syndrome

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ABSTRACT

We report the case of a 29 year old woman with a complex movement disorder syndrome due to the combination of coexisting pathological triplet repeat expansions of huntingtin and ATXN8 genes. The disease course was characterized by mental disturbances including cognitive decline and changes in personality starting at the age of 12 years, followed by twisting motions, intentional tremor and gait ataxia. Later Parkinsonian symptoms of micrographia, bradykinesia, muscle rigidity and mental decline became dominant. Brain MRI showed hypoplasia of the nucleus caudatus and generalized atrophy; MR spectroscopy revealed a decrease of all typical metabolites except for an increased level of lactate and acetate. Therapeutic trials with pramipexole, ropinirole and tetrabenazine showed no benefit, while levetiracetam caused agitation and hallucinations.

We discuss phenotype–genotype correlation and the rule of triplet repeat expansions of gene ATXN8.

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1. Introduction

Genetic findings in neurodegenerative disorders can help to increase our understanding of the molecular pathology of complex diseases. This can lead to more appropriate diagnosis, genetic counseling and the option of predictive testing. Furthermore, understanding the molecular basis may result in a change of classifications and offer new therapeutic approaches. The pathogenic role of triplet repeat expansions in the ATXN8 gene has been questioned as large CTA/CTG repeats have been reported in patients with spinocerebellar ataxia 8 (SCA8) [1] and in rare instances in normal controls too. The clinical symptoms include cerebellar ataxia, dysarthria, dysphagia, sensory neuropathy and cognitive impairment. The reported repeat lengths associated with ataxia usually range from 85 to 130 [2]. In neurodegenerative disorders such as sporadic Parkinson disease (PD) [2] and in ataxias like SCA1, SCA6, 16q-ADCA, and Friedreich's ataxia (FRDA) a rare coexistence of the repeat expansion in the ATXN8 gene has been observed [3–6]. On the basis of clinical data and neuropathological findings a common pathogenesis has been suggested for SCA6, SCA8 and 16q-ADCA [4]. In the case of 16q-ADCA plus SCA8 severe symptoms and early age of onset have been described [5]. To our knowledge, the coexistence of Huntingtin

disease (HD) and the mutation of ATXN8 gene have not been reported to date.

2. Clinical case

The birth history and childhood development of the 30 year old Hungarian woman were normal. School enrolment and development in the elementary classes were normal up to the age of 11 years. Subsequently, the disease course was characterized by mental disturbances including cognitive decline, changes in personality and disengagement starting at the age of 12 years. The first contact with our outpatient clinic was made at the age of 20 years. At this stage slight hypophonia, leg spasticity, trunk ataxia and left hand chorea were present. Slight psychomotor deceleration and decrease of initiative were observed as well. Her activity of daily living was not impaired. At the age of 21 years trunk ataxia had progressed slightly and dysidiadochokinesia was present. At age 24, chorea developed in all extremities accompanied by further psychomotor decline and loss of initiative. Despite the progressive disease, the patient remained independent in activities of daily living and employed until the age of 25. In the following year she had to give up employment due to rapid deterioration of movements, frequent falling due to moderate gait ataxia, disabling increase of tremor and twisting motions, spasticity in all extremities as well as Parkinsonian symptoms of micrographia, hypo- and bradykinesia. Muscle rigidity became dominant, her posture became inflected, and kyphoscoliosis was present. Aged

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28 years, her gait became broad-based, ataxia of trunk and all extremities were dominant. She went on to develop severe mental impairment and infantile emotional status the following year. Currently the main clinical findings are moderate spastic tetraparesis, moderate to severe chorea, ataxia, Parkinsonian symptoms, generalized myoclonus, vertical gaze palsy, dysphagia and dysarthria. Due to her severe impairments, comprehensive care has to be provided by her family. The family history is positive; the patient's grandmother, her mother and aunt all died at age of 30 to 40 years due to severe movement disorders. The father of our index patient is healthy as is her 3 years older brother and 5 year old paternal half-brother. In her first MRI at the age of 20 years, slight hypoplasia of the head of caudate was seen although MR spectroscopy at this stage was normal. In the brain MRI study 9 years later, hypoplasia of the nucleus

caudatus and generalized atrophy were present. MR spectroscopy showed neuronal dysfunction with decreased level of NAA and all other typical metabolites except lactate and acetate, which were slightly increased in the basal ganglia as described for Huntington disease previously [7] (Fig. 1). Electrophysiological studies like VEP, BAEP and ENG were normal, but EEG showed a desynchronized low voltage posterior basic rhythm but no epileptiform potentials. Lab tests including spinal fluid analysis were normal. Treatment with dopamine agonists like pramipexole (3 × 0.36 mg/day) or ropinirole (slow release SR, 2 mg/day) had no effect on Parkinsonian symptoms. Due to side effects like vertigo, sleepiness and agitation these treatments were not tolerated in the long term or in the appropriate doses. Tetrabenazine (2 × 25 mg/day) did not improve her choreiform movements significantly. Treatment with levetiracetam with

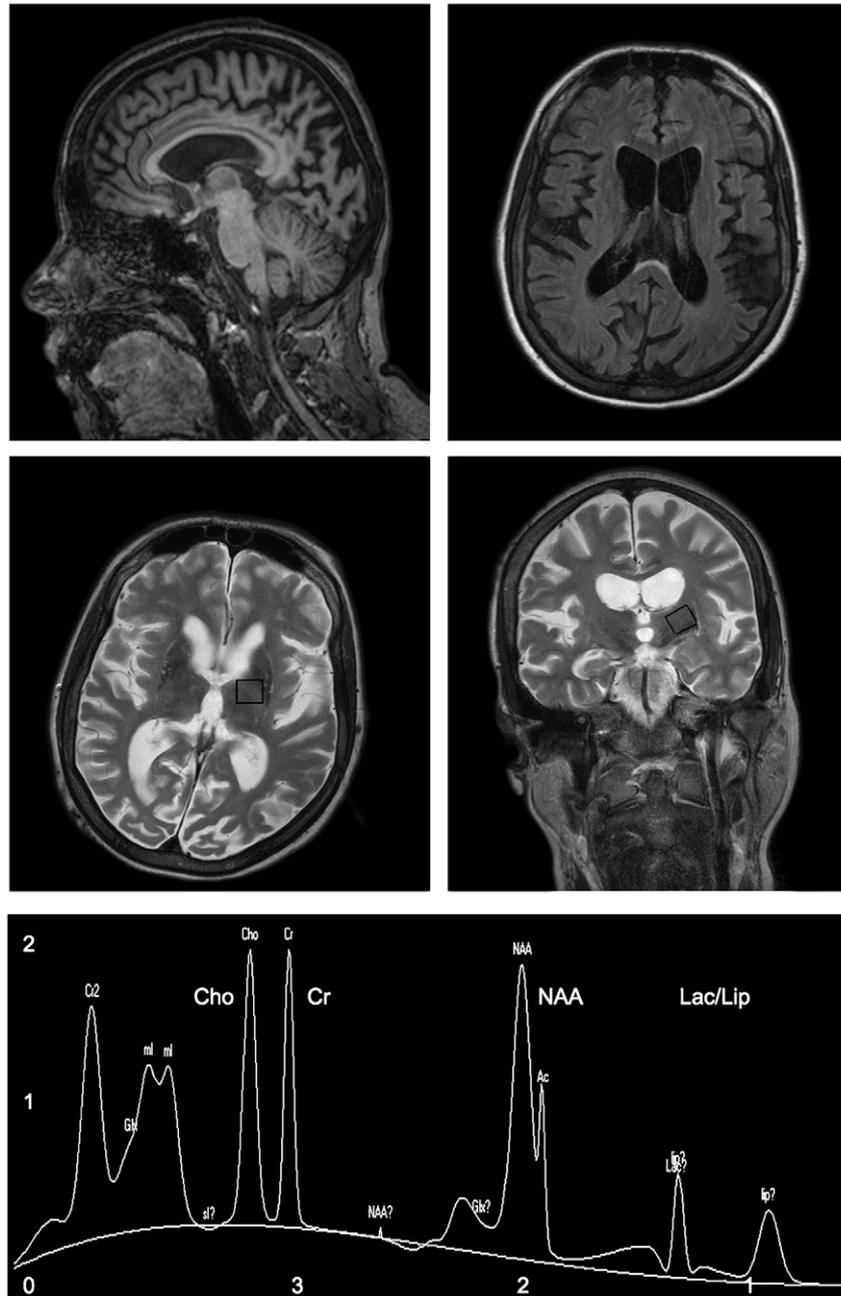


Fig. 1. Symmetrical moderately enlarged intracerebral and extracerebral liquor spaces maximal in the frontal part of the ventricles indicating atrophy of the caudate nuclei. The MR spectroscopy was performed in the region of the left caudate nucleus involving parts of the thalamus, internal capsule and nucleus lentiformis. N-acetylaspartate (NAA), choline, creatine were reduced. There was a slight increase of lactate, acetate and moderate increase of lipids as a sign of neurodegeneration.

Table 1

Genetic testing for repeat expansions were performed as summarised. This individual possesses the Huntington's disease CAG mutation and an SCA8 repeat expansion.

Test	Result	Normal	Borderline	Full mutation
SCA1	29 and 29	≤34	35–46	≥47
SCA2	22 and 22	≤31	32–35	≥36
SCA3	23 and 14	≤40	41–60	≥61
SCA6	13 and 13	≤18	19–20	≥21
SCA7	10 and 10	≤18	19–36	≥37
SCA8	104 and 25	≤50	51–109	110–250
SCA10	14 and 13	≤22	23–699	≥700
SCA17	36 and 36	≤42	43–46	≥47
DRPLA	16 and 8	≤35	36–48	≥49
HD	54 and 17	≤26	27–35 (36–39 reduced penetrance)	≥40

2×1000 mg resulted in improvement in the motor symptoms; the myoclonus disappeared but severe agitation and hallucinations occurred.

3. Genetic findings

The patient was positive for SCA8 possessing a 104 and 25 CTA/CTG repeats allele and positive for HD (IT15) possessing a 54 and 17 CAG repeats allele. Genetic testing of SCA1, 2, 3, 6, 7, 10, 17 and dentatorubral and pallidolusian atrophy (DRPLA) were normal. The number of repeats detected are summarised in Table 1 (Athena Diagnostics, Massachusetts, USA). Her older brother has declined genetic testing until now. Her father tested negative for HD and SCA8.

4. Discussion

SCA8 is a slowly progressive ataxia with disease onset typically in adulthood. The ATXN8OS (CTA)ⁿ(CTG)ⁿ composite repeat expansion is transmitted in an autosomal dominant manner with reduced penetrance [8]. Clinical symptoms are adult onset ataxia, dysarthria and clumsiness of gait and limb movements. Life span is not shortened typically [1]. The CTG expansion occurs at the 3' end of a processed non-coding RNA. The elongated expansions of the transcripts may cause a gain of toxic function of the RNA as described previously [9]. As there is an overlapping gene ATXN8, the polyglutamine expansion protein possibly contributes through toxic effects, too [10]. The clinical presentation of large repeat expansions is variable; the phenotype spectrum ranges from healthy subjects, patients with cerebellar ataxia to patients with typical and atypical Parkinson disease [2]. In addition coexistence with SCA1, SCA6, 16q-ADCA, FRDA have been reported. In these rare cases the coexisting genetic abnormalities were related to more severe and early onset of symptoms [3–6].

Huntington disease is a CAG trinucleotide repeat disease resulting in choreiform movements and dementia. There is an established inverse correlation between CAG repeat length and age of onset. Patients with juvenile onset have CAG expansions greater than 60 [11]. The polyglutamine strand confers a toxic gain of function but the mutation also exerts a dominant negative effect [12].

The coexistence of HD and SCA8 mutations resulted in our case in a more severe form of movement disorder and dementia syndrome. The expansion size of 54 is usually seen in adult onset HD. Severe ataxia with inability to walk independently is usually not a typical feature for HD or SCA8 at this disease stage. Wu et al. detected SCA8 expanded alleles in PD and atypical Parkinsonism suggesting that SCA8 CTG repeat expansion may play a role in the development of sporadic PD or atypical Parkinsonism [2]. The fact that Parkinsonian symptoms of our patient remained unresponsive to dopaminergic medication supports the hypothesis of possible involvement of SCA8 in the pathogenesis of atypical Parkinsonism.

We assume that both the RNA gain-of-function mechanism involving CUG expansion RNAs [13], and the polyglutamine expansion protein due to the SCA8 mutation play a role in the development of the disease. Additionally the mutant huntingtin can affect several nuclear and cytoplasmic proteins that regulate transcription [14], apoptosis [15], mitochondrial function [16], vesicular and neurotransmitter release and axonal transport [17] through a toxic gain of function as well as a dominant negative effect, in which it interferes with the typical function of wild-type huntingtin [12]. These disease mechanisms are likely to contribute in a cumulative way to the pathology of this severe, combined repeat expansion disorder.

References

- [1] Koob MD, Moseley ML, Schut LJ, Benzow KA, Bird TD, Day JW, et al. An untranslated CTG expansion causes a novel form of spinocerebellar ataxia (SCA8). *Nat Genet* 1999;4:379–84.
- [2] Wu YR, Chen IC, Soong BW, Kao SH, Lee GC, Huang SY, et al. SCA8 repeat expansion: large CTA/CTG repeat alleles in neurological disorders and functional implications. *Hum Genet* 2009;125:437–44.
- [3] Sulek A, Hoffman-Zacharska D, Zdzienicka E, Zaremba J. SCA8 repeat expansion coexists with SCA1 – not only with SCA6. *Am J Hum Genet* 2003;73:972–4.
- [4] Izumi Y, Maruyama H, Oda M, Morino A, Okada T, Ito H, et al. SCA8 repeat expansion: large CTA/CTG repeat alleles are more common in ataxic patients, including those with SCA6. *Am J Hum Genet* 2003;72:704–9.
- [5] Ohnari K, Aoki M, Uozumi T, Tsuji S. Severe symptoms of 16q-ADCA coexisting with SCA8 repeat expansion. *J Neurol Sci* 2008;273:15–8.
- [6] Corral J, Genis D, Banchs I, Nicolás HS, Armstrong J, Volpini V. Giant SCA8 alleles in nine children whose mother has two moderately large ones. *Ann Neurol* 2005;57:549–53.
- [7] Reynolds NC, Prost RW, Mark LP, Joseph SA. MR-spectroscopic findings in juvenile-onset Huntington's disease. *Mov Disord* 2008;23:1931–5.
- [8] Mosemiller AK, Dalton JC, Day JW, Ranum LP. Molecular genetics of spinocerebellar ataxia type 8 (SCA8). *Cytogenet Genome Res* 2003;100:175–83.
- [9] Philips AV, Timchenko LT, Cooper TA. Disruption of splicing regulated by a CUG-binding protein in myotonic dystrophy. *Science* 1998;280:737–41.
- [10] Moseley ML, Zu T, Ikeda Y, Gao W, Mosemiller AK, Daughters RS, et al. Bidirectional expression of CUG and CAG expansion transcripts and intranuclear polyglutamine inclusions in spinocerebellar ataxia type 8. *Nat Genet* 2006;38:758–69.
- [11] Brinkman RR, Mezei MM, Theilmann J, Almqvist E, Hayden MR. The likelihood of being affected with Huntington disease by a particular age, for a specific CAG size. *Am J Hum Genet* 1997;60:1202–10.
- [12] Walker FO. Huntington's disease. *Lancet* 2007;369:218–28.
- [13] Ranum LP, Cooper TA. RNA-mediated neuromuscular disorders. *Annu Rev Neurosci* 2006;29:259–77.
- [14] Cha JH. Transcriptional dysregulation in Huntington's disease. *Trends Neurosci* 2000;23:387–92.
- [15] Hickey MA, Chesselet MF. Apoptosis in Huntington's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27:256–65.
- [16] Panov AV, Burke JR, Greenamyre JT. In vitro effects of polyglutamine tracts on Ca²⁺-dependent depolarization of rat and human mitochondria: relevance to Huntington's disease. *Arch Biochem Biophys* 2003;410:1–6.
- [17] Charrin BC, Saudou F, Humbert S. Axonal transport failure in neurodegenerative disorders: the case of Huntington's disease. *Pathol Biol* 2005;53:189–92.